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Dated 31 August 2004

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1/77

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P01/7700 0.00-0325060.2

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THE PATENT OFFICE
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27 OCT 2003
LONDON

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

27 OCT 2003

The Patent Office

Cardiff Road
Newport
Gwent NP9 1RH

1. Your reference SP/LT/N14820

2. Patent application number *(The Patent Office will fill this part)* 0325060.2

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

LOMBARD MEDICAL PLC
Sheffield Technology Park
60 Shirland Lane
Sheffield S9 3SP, United Kingdom

Patents ADP number *(if you know it)* 08741225001

If the applicant is a corporate body, give the country/state of its incorporation

4. Title of the invention

Drug Release System

5. Name of your agent *(if you have one)* Williams Powell

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*
Morley House, 26-30 Holborn Viaduct
London
EC1A 2BP

Patents ADP number *(if you know it)* 5830310001 ✓

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application.

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(answer 'Yes if:*
a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

Yes

ıtents Form 1/77

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Continuation sheets of this form	
Description	4
Claim(*s*)	0
Abstract	0
Drawing(*s*)	1 + 1 R

0. If you are filing one of the following, state how many against each item.

Priority documents	None
Translations of priority documents	None
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	None
Request for preliminary examination and search *(Patents Form 9/77)*	None
Request for substantive examination *(Patents Form 10/77)*	None
Any other documents *(please specify)*	None

11. I/we request the grant of a patent on the basis of this application.

Signature [signature] Date 27 October 2003

12. Name and daytime telephone number of person to contact in the United Kingdom: Mr Lee Anderson 020 7936 3300

Warning

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Notes

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b) *Write your answers in capital letters using black ink or you may type them.*

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DRUG RELEASE SYSTEM

The present invention relates to the incorporation of more than one bioactive agent into a coating composition and a method for using the composition to coat an implantable medical device.

It is known to apply biologically active materials to the surface of an implantable medical device such as a stent, see for example WO 03/024500. Such an arrangement constitutes the subject matter of co-pending patent application 0319461.0.

The application of drug combinations to stents is also disclosed in WO 01/87372. Example 6 relates to spraying a stent with a solution of poly (ethylene-covinyl acetate), polybutyl methacrylate and rapamycin dissolved in tetrahydrofuran followed by spraying the thus-coated stent with a solution of poly (ethylene-covinyl acetate) polybutyl methacrylate and dexamethasone dissolved in tetrahydrofuran.

The present invention seeks to provide an improved release system for implantable devices. Preferred aspects of the present invention seek to provide a system in which drugs or other biologically active materials are released in a controlled manner, i. e. at a desired rate and/or over a desired period of time and/or after a predetermined period of time after implantation of the device.

According to a first aspect of the present invention there is provided an implantable medical device having thereon a first coating of a first biologically active material in a first carrier material and a second coating of a second biologically active material in a second carrier material.

The two carrier materials are preferably mixtures of polymers and may comprise the same two polymers in different proportions by weight.

The proportions by weight may be selected so that the second biologically active material is released relatively quickly and the first biologically active material is released in a controlled manner and/or relatively slowly.

In one embodiment, the carrier material is a single polymer, the other carrier material being a mixture of this polymer with another polymer.

According to a second aspect of the present invention there is provided a method of treating an implantable medical device comprising the steps of coating at least part of the device with a first biologically active material in a first carrier material and coating at least part of the device with a second biologically active material in a second carrier material.

The coatings are preferably applied by spraying or dipping, and the second coating is preferably applied over part or all of the first coating.

The first coating may be an anti-proliferative agent such as rapamycin and the second coating may be an anti-inflammatory agent such as dexamethasone.

Preferred embodiments of the present invention will now be described, by way of example only, with reference to the accompaying drawings, of which:

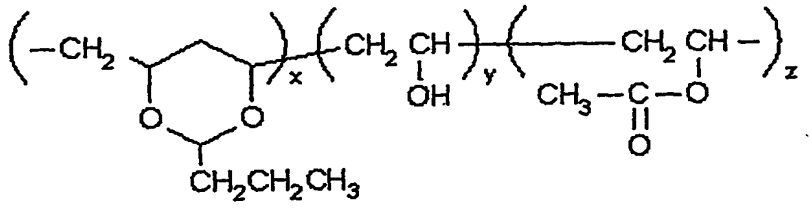
Fig. 1 is an enlarged sectioned view of part of a stent in accordance with a first embodiment of the present invention; and

Fig. 2 to 4 are similar views, respectively, of stents in accordance with second, third and fourth embodiments of the present invention.

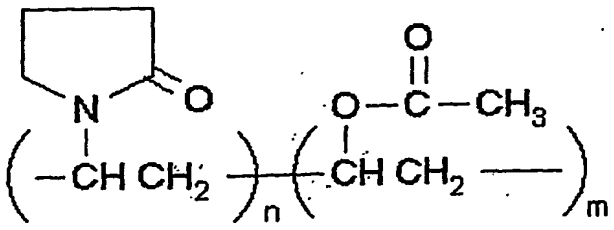
Referring to the drawings, Fig. 1 shows part of the wall 11 of a stent 10 of metallic material. To solve clinical problems, such as restenosis, produced by the implanting of the stent 10, it is treated as follows.

It is coated with a first layer 12 by spraying or dipping with rapamycin in a mixture of the two polymers poly(vinyl butyral-co-vinyl alcohol-co-vinyl acetate) (PVB) and poly (1-vinylpyrrolidone-co-vinyl acetate) (PnVPA). The structures of these polymers are:

1. Poly(vinyl butyral-co-vinyl alcohol-co-vinyl acetate) (PVB)



2. Poly(1-vinylpyrrolidone-co-vinyl acetate) (PnVPA)



Layer 12 typically has a thickness of 1 micron. The rapamycin is provided in a suitable solvent which, after the application of layer 12, is removed by allowing the coating to dry. The drying operation also serves to maintain the activity of the rapamycin.

The stent is then similarly coated until a second layer 14 comprising dexamethasone in a mixture of the same two polymers. In this layer, the polymers PVB and PnVPA have different proportions by weight than in layer 12. Layer 14 typically has a thickness of 1 micron. The dexamethasone is provided in a suitable solvent which, after application of layer 14, is removed by drying.

The formulations of layers 12 and 14, and in particular the ratios of the polymers PVB and PnVPA, are selected to release their active agents at respective desired rates. As the dexamethasone is in the outer layer 14, it will be released first into the patient's body. The ratio of PVB, which is hydrophobic, to PnvPA, which is hydrophilic, is selected so that the dexamethasone is substantially released during the first few hours after implantation to reduce inflammation. Release of the dexamethasone, normally at a reducing rate, may continue for a period of up to ten days. Typical ratios for PVB to PnVPA in layer 14 are between 70:30 and 94:6, preferably 90:10.

The rapamycin in the lower layer 12 is released more slowly. Typical percentages by weight of PVB are 80% to 100%, i.e. layer 12 may be solely PVB with no PnVPA content. The preferred ratio of PVB to PnVPA is 98:2. The rapamycin is typically released over a period of ten days or more. An advantage of the above-described arrangement is that it achieves a selective-release and the right dose of a bioactive agent from each layer of the coating composition over a specified period of time. By independently varying the compositions of the polymer mixtures, the thicknesses of the layers and the concentration of the biologically active materials in the respective layers, the selective release of the active materials can be carefully controlled with reference to rate of release, duration of release and timing of initiation of release.

Various modifications may be made to the above-described arrangement. For example, the thickness of layers 12 and 14 may vary between 0.1 and 10 microns and may have different values in a single stent.

Instead of rapamycin, they may be used as the anti-proliferative agent estradiol, taxol, vincristine, vinblastine, or a nitric oxide donor. Appropriate mixtures of drugs may be incorporated in each of layer 12 and 14.

A primer layer (not shown) may be applied to the surface of stent 10 before the application of layer 12.

Other carrier materials may be used instead of the polymer mixtures disclosed above.

Preferably the entire surface of stent 10 is coated, but if desired parts of its surface may remain uncoated.

Preferably layer 14 covers all layer 12, but to achieve certain patterns of release, parts of layer 12 may remain uncoated.

Figure 2 shows a stent 20 in accordance with a second embodiment of the present invention in which an intermediate layer 21 in provided between layer 12 and 14. Layer 21 comprises a drug-free mixture of the polymers PVB and PnVPA which introduces an additional delay before the active material is released from layer 12. Typically the proportion of PVB is higher in layer 21 than in both layers 12 and 14, but this is not essential. To achieve certain patterns of release the proportion of PVB in layer 12 may be lower than in layer 14.

As shown in Figure 3, a stent 30 in accordance with a third embodiment has a barrier layer 31 provided over layer 14. Layer 13 serves to protect the underlying coatings. In a modification, a stent may have both an intermediate layer 21 and a barrier layer 31.

In a stent 40 according to a fourth embodiment of the present invention, to achieve a different pattern of release, layers 12 and 14 are applied to different regions of the wall 11 of the stent.

The stents may be made of a plastics material.

The features and modifications of the various embodiments may be interchanged or combined as desired.

The drug-eluting coatings disclosed can be used with coronary, peripheral or gastrointestinal stents or with other types of devices such as abdominal aortic aneurysm devices, anastomosis devices, heart valve repair devices, implantable biosensors, pacing and electro stimulation leads, vascular grafts or vena cava filters.

Other drugs may be used instead of those disclosed, including anti-platelet agents e.g prostaglandins and/or anti-coagulants agents e.g. heparin.

To release three or more biologically active materials, implantable devices are coated with three or more layers and such arrangements combine as desired the features of the various described embodiments.

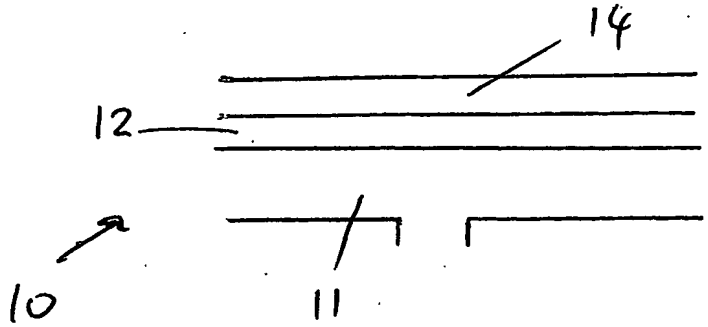


Fig 1

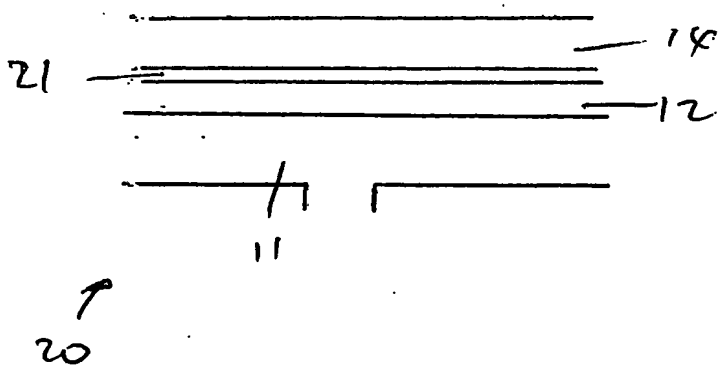


Fig 2

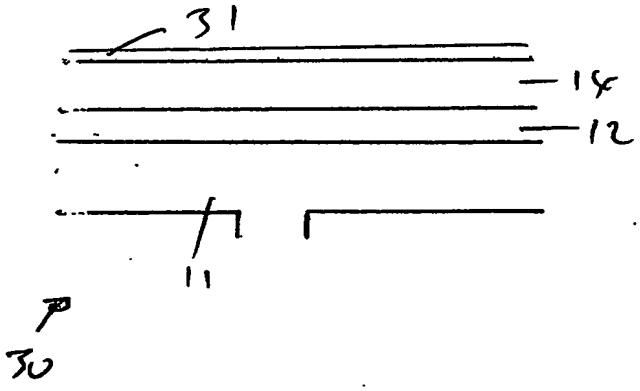


Fig 3

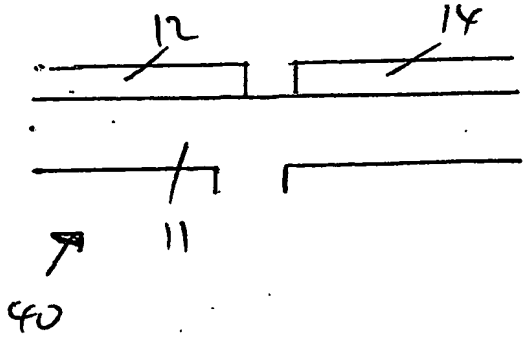


Fig 4

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